IS THE CONTROL OF EMBRYONIC DEVELOPMENT A PRACTICAL PROBLEM?

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Under favorable natural conditions two normal parents should, and usually do, produce a vigorous normal offspring. When, however, the conditions of development are modified or if in the second place the parents are not entirely normal the offspring is usually more or less defective. I shall attempt to show that the proper development of the offspring is dependent upon two main factors, first the physical qualities of the parental germ cells, and second the environment in which the embryo develops.

One is at first sight apt to think that deformities and defects are rare among men and other animals; but closer observation will show that the really structurally perfect individual is rather exceptional. Gross anatomical defects or monstrosities are frequently found among all animals, while lesser defects of minor importance are to be observed in a majority of individuals. These defects often cause no inconvenience, and indeed, we may be ignorant of their presence, since they are generally internal. Yet many apparently normal individuals sooner or later suffer or may actually die from some hidden developmental imperfection. The well-known congenital defects of the heart and other parts of the vascular system, digestive tract, etc., as well as the numerous developmental arrests in various parts of the body constantly remind the observer of the great loss in ability and energy that the race suffers as a result of faulty development.

These defects in construction must be considered a disease which causes the death of about 23 per cent. of the human race before or shortly after the time of birth (Sullivan's studies and French statistics), and handicaps a certain proportion of the survivors through-

out their lives. We carefully study and use all known precautions to protect ourselves against post-natal infections and diseases, and much interest and time is given to combating the causes, yet little is said and scarcely anything done towards a control of development, or the hygienic protection of the developing individual.

This is really a morphological problem and is as truly a part of the fight against disease as is the treatment of abnormal physiological processes. It is not all of morphology to describe and study the detail of bodily structure, but its important task is to understand and analyze that structure, and if possible control and regulate its formation: and thus, if properly developed its goal is to relieve the race of its great structural disease—a disease which affects more individuals than any other one malady of man.

To most persons the above task seems at first thought a futile undertaking, and any one suggesting such control or preventive treatment might be interpreted as indulging in fanciful speculation. Yet the data available from the studies of defective persons in different countries of the world, and the experimental evidence furnished by work on lower animals makes the correction or prevention of developmental defects seem even today a problem to be practically handled to a slight degree at least.

To proceed as with any other disease, we must first ascertain the cause of these conditions, as the possibility of a cure depends upon the nature of the cause.

Are monstrosities and defective development due to some innate change within the germ cells of the parent, thus being incurable, as many former workers would have us believe? Or, are they due to changes produced in the germ cells by the action of some unusual condition in the body of either the male or female parent, or finally may they not be due to an unusual environment acting upon the developing embryo itself? In both of the latter cases the conditions are open to regulation or control. These questions may only be solved experimentally and the experiments have proven that the great majority of monsters are due to the action of unusual conditions upon either the parental germ cells or the developing embryo. There may be some changes of form or variations in animals which are due to

innate changes in the germ-plasm but even these when fully understood may possibly be shown to result indirectly from some change in the chemical surroundings.

First to consider the modifications induced in the developing egg or embryo by a strange chemical environment. It has been found for the eggs of a number of animals that develop normally in sea-water that when certain chemicals are added to their environment they develop into various unusual forms.

I experimented for several years on fish's eggs and found that on adding any one of a large series of salts to the sea-water that the eggs developed abnormally and gave rise to a great number of monstrous individuals. The types of the monstrosities were variable, and the same kind of monster often resulted from different treatments. This was to be expected, but the important problem was to produce some definite type of monster in great numbers with any given treatment. This I finally succeeded in doing and in some experiments got as many as 90 per cent. typical cyclopean or monophthalmic monsters. These types of monsters first occurred in solutions of $MgCl_2$ in sea-water. In such solutions as many as 50 in 100 eggs formed one-eyed cyclopean embryos. Since Mg has the power to inhibit activity in animals and so acts as an anæsthetic I determined to try the action of a number of such substances on the developing eggs to ascertain whether they might also inhibit the lateral migration of eye parts. Alcohol, ether, chloroform, chloreton, etc., were employed and cyclopean monsters resulted from eggs developing in all of these substances. Alcohol gave the most decided effects and inhibited the normal production of eyes in almost all cases. All of these anæsthetics act more particularly upon the central nervous system of the adult and it is important to find that the development of the nervous system is also especially affected by them. In alcohol solutions the embryos showed almost every gross abnormality of the brain which is known to occur, and the spinal cord was often defective.

I have repeated the experiments of Féré with hen's eggs and find that when these eggs are exposed to fumes of alcohol many abnormal chicks result. When hen's eggs are placed in closed dishes over

evaporating 95 per cent. alcohol enough of the fumes penetrate the shell and enter the contents of the egg to cause the developing chick to form abnormally.

McClendon has lately found that an excess of CO_2 and other substances also cause cyclopia and brain abnormalities. Many other workers have shown the effects of the environment on the developing egg.

It is, therefore, proven that the experimenter has the power to take an egg which would normally give rise to a perfect animal and by proper treatment he may cause it to form a typically abnormal individual. The monster may in many cases be able to survive and move about. No one can question that in these experiments the unfavorable environment modifies the form of the resulting individual.

Does this also occur in embryos developing in the mother's body? Children are born which exhibit the same types of deformities as those described above. Syphilitic mothers usually abort or give birth to abnormal children and there is much evidence to indicate that an alcoholic mother is more apt to produce an abnormal child than is a non-alcoholic mother.

Tubal pregnancies are common among women with venereal diseases and in such cases the embryo must necessarily develop under abnormal environment, having a poor surface for placental attachment in a region not adapted to the conditions of pregnancy. The conditions for embryonic nutrition are poor. Mall has found that while only 7 per cent. of uterine pregnancies in his records contained pathological embryos, that 96 per cent. of the embryos in tubal pregnancies were pathological, only 2 in 46 specimens being normal. This is strongly indicative of an abnormal environment as the cause of abnormalities. If these monsters were due to inherent tendencies in the germ cells one should not expect more abnormal tubal than uterine embryos.

Among lower mammals it has been shown that dogs fed on alcohol produce deformed and otherwise defective pups. I am now conducting a series of experiments with guinea pigs which show that a female treated with alcohol during her pregnancy will often

abort or produce defective young, while the control animals are giving birth to normal young. Many more cases could be cited if time permitted.

Experiments on lower animals, therefore, show and human statistics seem to indicate that the cause of structural disease is often an abnormal developmental environment. To prevent such a disease the developmental conditions must be controlled and rendered as nearly normal as possible.

The second consideration is whether abnormal chemical environment may act on the parental germ cells in such a manner as to cause them to change and become incapable of giving rise to a normal individual. It is well known that certain disease toxins such as that of syphilis and substances such as alcohol and lead effect various body tissues so as to render them unfit for normal physiological activity. It is, therefore, only logical to suppose that the same or similar substances may effect the germ cells and so derange their chemical constitutions as to cause them to give rise to offspring of peculiar structure and qualities.

Bertholet has found that alcohol has a particular affinity for the reproductive glands just as it does for the nervous system. In examining the structure of the testicles from a large number of chronic alcoholics it was shown that spermatozoa were absent entirely or degenerate in form (azoospermy) in a majority of the cases. It is doubtless true that the ability of the spermatozoa to accomplish normal fertilization would be affected long before any definite structural change could be observed.

The crucial case is the treatment of the male in such a way as to render his spermatozoa unable to produce a normal development when combined with a healthy egg from a normal female. In this case the action must of necessity be on the germ cell only and not on both the egg and embryo as it might be in treating a female mammal.

It must be recognized that an individual owes its structure and character to the peculiar chemical constitution of the germ cells from which it arises. The germ cells of two species of animals are

probably as different chemically as the animals are morphologically. Therefore, if the chemical nature of the germ cells is disturbed or injured by the action of poisons in the animal's blood they will probably show this injury in the type of individual to which they give rise.

Constantine Paul long ago found in studying 88 cases of pregnancy among women lead workers that 71 resulted in abortion, premature labour, or stillbirth while only 17 children were born alive and of these five died within the first year. Several of these women later produced healthy children after leaving this work. (This indicates that when the cause is known for defective development the cure may often be established by its removal.) Lead not only effects the developing fœtus but also acts directly upon the germ cells as is shown in the case of men working in lead while their wives were not exposed to the poison. Many of the offspring from such fathers are aborted and the children born are epileptic, feeble-minded or generally defective.

To return to the results furnished by the guninea pig experiments referred to above—I have chosen healthy individuals and treated them daily with the fumes of 95 per cent: alcohol to about the point of intoxication. Feeding alcohol and giving it by stomach tube was first tried, both of these methods were unsatisfactory as the guinea pigs did not take alcoholic food in sufficient quantity and the stomach tube disturbed the animals to such a degree that I feared the experimental result might be vitiated even though it could be partially controlled. The inhalation method is perfectly satisfactory; the animals are placed in a copper tank having a screen floor which holds them above the evaporating alcohol. The alcohol is breathed directly into the lungs and affects the animals readily, in much the same manner as weak treatments of ether or chloroform would. The animals are thus put into a condition of chronic alcoholism, being almost intoxicated six times per week. Many of these guinea pigs have been killed and their lungs, liver and other organs examined and found to be perfectly normal so far as their appearance goes. The conjunctiva over the eyes is very often affected by the fumes, during the beginning of the treatment the eyes often

become white, this is transitory in most instances and the eyes finally clear again and remain in a normal condition from then on. Most of the specimens have fattened under the alcohol treatment.

The matings have been made in such a fashion as to test several questions. First, alcoholic males are mated with normal females, paternal influence, the crucial test for the effect upon the germ cells. Second, alcoholic females are paired with normal males, the maternal influence plus the direct action on the developing embryo. Lastly, alcoholic males and females are paired.

The results of 40 such matings are shown in Table I. The decided effects of the alcoholic treatment are seen when the records are compared with those of the normal guinea pigs.

TABLE I.

MATINGS OF ALCOHOLIZED GUINEA-PIGS.

Condition of Animal.	Number of Matings.	No Result or Early Abortion.	Stillborn Litters.	Number of Stillborn.	Living Litters.	Early Deaths.	Surviving Young.
Alc. male × nor. female	24	14	5	8	5	5	5 1 + 4
Nor. male × alc. female.....	2	1	0	0	1	0	1 Preg. 2 in utero, 1 deformed.
Alc. male × alc. female.....	14	10	3	5	1	1 died 6th day	0
Summary.....	40	25	8	13	7	6	6 6 in 25
Nor. male × nor. female. *Control.*	8	0	0	0	8	0	15 15 in 15

In the 24 cases in which normal females were mated with alcoholic males, 14 gave negative results. Some of these probably aborted early as the parents were all fertile and the female is apt to eat the young before they have been observed when they are born prematurely. Five of the matings gave stillborn young, in some cases they were born a little before term. Litters were born alive but the young died soon after showing many nervous symptoms, such

as epileptic-like seizures, and all died in convulsions. Only two litters consisted of normal offspring and these young, five in all, seem healthy though unusually small. It is thus seen that in 24 matings of *normal* females with alcoholic males only two gave normal results. Whereas in the control animals all matings have resulted in the production of normal offspring.

Only two matings were made between normal males and alcoholic females. One of these gave no result or was possibly aborted very early and lost, while the other mating produced one female offspring that lived to become pregnant by an alcoholic male. This last mentioned female was killed by accident, two embryos were found *in utero* one of which was deformed.

Fourteen matings were made between alcoholic males and females. Ten gave no result or aborted very early and were eaten, while four cases showed the following records. One young was born weak and died in convulsions on the sixth day after birth. Two cases of premature births of dead young. One female had young *in utero* when killed.

TABLE II.

Successive Matings of Ten Females.

Animal.	1st Mating.	2d Mating.	3d Mating.	4th Mating.
No. 10 alc.	Alc. male 4 = 1, young died 6th day.	Alc. male 4 = 0.	Alc. male 6 = 0.	Alc. male 4 = 1, embryo in utero 2nd week.
No. 12 alc.	Alc. male 5 = 0.	Alc. male 5 = 0.	Alc. male 4 = 0.	
No. 11 alc.	Alc. male 6 = 0.	Alc. male 6 = 0.	Alc. male 5 = 2, premature, still-born.	Alc. male 4 = 0.
No. 13 nor.	Alc. male 5 = 1, stillborn.	Alc. male 5 = 0.	Alc. male 4 = 0.	
No. 17 nor.	Eth. male 1 = 0.	Eth. male 1 = 0.		
No. 18 nor.	Alc. male 5 = 0.	Alc. male 5 = 0.	Alc. male 6 = 0.	
No. 7 nor.	Eth. male 2 = 2, premature, stillborn.	Eth. male 2 = 0.	Eth. male 2 = 0.	
No. 14 nor.	Eth. male 3 = 0.	Eth. male 3 = 0.		
No. 19 nor.	Alc. male 4 = 0.	Alc. male 6 = 1, stillborn.	Alc. male 6 = 0.	Alc. male 5 = 4, small but active.
No. 15 nor.	Alc. male 6 = 2, stillborn.	Alc. male 5 = 0.	Alc. male 5 = 2, died 4th week.	Nor. male = 1, normal young.

These results stand in marked contrast to the records of the control, which show all normal conceptions and normal offspring.

The second table shows the results of successive matings in ten of the females. The varying success of the conceptions in the same individual are striking.

Nice has quite recently recorded a similar series of experiments with alcohol on mice. Alcohol was given to the mice in their food. Nice finds that while there was a certain fatality among the offspring from alcoholic parents as compared with those from normal parents, where there was no fatality, yet nevertheless the offspring of alcoholic parents actually grew faster than those from the control. This may indicate that alcohol is not equally poisonous in its effects upon all animals, as might really be expected. The germ cells of mice may be more or less immune to the action of alcohol. It is well known that the action of alcohol is different in its effects on individuals from different human families. Some alcoholics show chiefly nervous disorders, hallucinations, delirium, etc., while others may have no nervous symptoms but exhibit various derangements of the digestive glands, kidneys, etc., or may have a fatty degeneration of almost all organs.

Finally it may be concluded that the experimental evidence goes to show that the development of an offspring may be modified by either treating the parents so as to affect their germ cells or by subjecting the developing embryo itself to unusual or injurious conditions.

The causes of many congenital defects are therefore known. It is possible to control embryonic development to such an extent as to produce abnormal structures. May not the proposition be reversed and unfavorable environments be treated in such a manner as to render them favorable to normal development? Diseased mothers may in some cases, at least, be made fit for the function of reproduction.

The regulation of structural disease becomes then a problem of morphology and hygiene. It is most important, and must precede,

or go before, the selective mating of human beings or the eugenics movement. The most intellectual will rarely submit to direction in choosing a mate, yet every productive pair will welcome any possible means of improving the quality of their offspring.

While preventive measures are being used to protect the post-natal life of the individual, why not guard as far as possible its pre-natal development?

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